(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 895 780 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
10.02.1999 Bulletin 1999/06

(51) Int Cl.[6]: **A61K 9/22**, A61K 47/38, A61K 31/135

(21) Application number: **98305529.4**

(22) Date of filing: **10.07.1998**

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: **31.07.1997 US 903019**

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(54) Extended release tablets particularly containing pseudoephedrine hydrochloride

(57) This invention relates to extended-release tablets particularly containing pseudoephedrine hydrochloride. The tablets comprise a sustained release hydroxypropyl methylcellulose matrix, a microcrystalline cellulose disintegrant, and a filler and are formed by a dry granulation, direct compression method. A method for forming these tablets is also disclosed.

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Description

BACKGROUND OF THE INVENTION

[0001] The advantages of sustained release products are widely recognized in the art and are of extreme importance in the pharmaceutical field. Through the use of such products, orally administered medications can be delivered continuously at a uniform rate over a prolonged period of time so as to provide a stable, predetermined concentration of drug in the bloodstream, without requiring close monitoring and frequent re-administration.

[0002] The sustained release character of such products is achieved by one of two methods: 1) providing a sustained release coating upon tablets or microspheres wherein slow release of the active occurs via either gradual permeation through or gradual breakdown of this coating or 2) providing a sustained release matrix, such as a fat, a wax, or a polymeric material intermixed with the active ingredient in the tablet itself. See, e.g., Manford Robinson, "Sustained Action Dosage Forms" in The Theory and Practice of Industrial Pharmacy, ch. 14 (L. Lachman et al., eds., 2d ed., 1976)

[0003] Such sustained release matrix formulations are typically prepared by methods involving pre-granulating the active ingredient together with the matrix material via a wet granulation, solvent granulation, shear-melt or roto-melt granulation, or a wet pre-adsorption technique. In these techniques, a liquid phase is used in order to uniformly mix and/or closely contact the ingredients together so as to provide an evenly distributed matrix in intimate association with the active ingredient. These formation processes help prevent creation of interspersed quick-release zones which would result in discontinuous dissolution of the tablet and thus cause bioconcentration spikes of active ingredient in the patient. They frequently also result in granules of a relatively higher density than dry granulated ones, thus allowing -- upon compression -- the production of tablets, for a given dose, that are smaller than those made by dry granulation for the same intended release rate.

[0004] However, these liquid phase methods require a multiplicity of steps and equipment for storage, handling, and dispensing of liquids, for drying, and/or for heating of the ingredients. When the liquid is water, its volume must be very carefully controlled so as to prevent any disintegrant in the formula from swelling; when the liquid is a volatile organic solvent, additional precautions must be taken to address the risks of fire, explosion, and worker exposure. Where a melt processing technique is used, heating presents a risk of inactivation of at least some of the active material and is incompatible for use with some active ingredients.

[0005] Thus, dry granulation has sometimes been used to form sustained release matrix tablets. This technique involves pre-granulating the matrix material with the active ingredient without the use of added liquids or heat. For example, U.S. 4,259,314 to Lowey employs a mixture of hydroxypropyl methylcellulose ("HPMC") and hydroxypropyl cellulose to form a sustained release matrix in which the cellulose ether mixture has a weighted average viscosity rating of 2504500cps, and preferably 1200-2900cps. These are equilibrated under an atmosphere having up to 40% relative humidity and then premixed together before drying to a moisture content of 1 % or less. The active and other ingredients -- after they have equilibrated under ≤40% humidity -- are combined with the cellulose ether mixture and the resulting combination is compressed at ≤40% humidity to produce a tablet.

[0006] U.S. 5,451,409 to Rencher et al. discloses a dry granulated pseudoephedrine tablet in which a mixture of hydroxypropyl cellulose and hydroxyethyl cellulose forms the sustained release matrix; 0.5-10% HPMC is also added as a binder.

[0007] U.S. 5,085,865 to Nayak discloses a two-layer tablet wherein one layer comprises a 60mg pseudoephedrine controlled release matrix formulation. The matrix or "sustained release agent" comprises hydroxypropyl and/or hydroxyethyl cellulose and, preferably also, sodium croscarmelose; this agent is present in an amount equivalent to at least twice that of pseudoephedrine. Up to half of the cellulose ether component may consist of HPMC. This layer may be formed using a dry granulation process.

[0008] However, none of these earlier formulations has produced a dry granulation, direct compression tablet employing a single polymer, HPMC controlled release matrix, which is able to provide sustained bioavailable concentrations equivalent to that of, e.g., wet or melt granulated, 12 hour release products. As a result, the efficiency and economy of production afforded by such a dry granulation, direct compression process have not been achieved for such formulations in general nor for pseudoephedrine formulations in particular.

SUMMARY OF THE INVENTION

[0009] The present invention relates to pseudoephedrine hydrochloride extended-release tablets which comprise a sustained release HPMC matrix, a microcrystalline cellulose disintegrant, and a filler and which are formed by a dry granulation, direct compression method. The HPMC of the invention has a molecular weight below 50K and a hydroxypropyl content of less than 9% by weight. A method for producing such tablets is also disclosed.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0010] In a preferred embodiment of the present invention, an active ingredient is first mixed together with a glidant and a filler and, after mixing, the combination is milled. Preferably, the active ingredient is pseu-

doephedrine or a pharmacologically acceptable salt thereof, such as pseudoephedrine hydrochloride or pseudoephedrine sulfate. Most preferred is pseudoephedrine hydrochloride. About 120mg per tablet of the active ingredient is used.

[0011] The glidants, fillers, and other excipients that may be used in the preferred embodiments include those described, e.g., in Handbook of Pharmaceutical Excipients (J.C. Boylan, et al., eds., 1986) and/or H.A. Lieberman, et al., Pharmaceutical Dosage Forms: Tablets (2d ed. 1990). Preferred glidants include colloidal silica and precipitated silica. A preferred colloidal silica is Cab-o-Sil® produced by the Cabot Corp. of Boston, MA; a preferred precipitated silica is Syloid® produced by W.R. Grace Co. of New York, NY. Preferably, about 0.2-2% by weight of glidant, based on the final weight of the composition, is employed. Where colloidal silica alone is used, the final composition will preferably comprise about 0.2-0.8% by weight glidant, more preferably about 0.25-0.75%.

[0012] Preferred fillers include calcium salts and sugars, for example, calcium phosphates, calcium sulfates, mannitol, lactose, and mixtures thereof. More preferred fillers include dicalcium phosphate, tribasic calcium phosphate, directly compressible calcium sulfate, directly compressible mannitol, anhydrous lactose, flowable lactose (e.g., Fast Flo® lactose produced by Foremost Farms USA of Baraboo, Wisconsin), and mixtures thereof. Most preferred is dicalcium phosphate. Preferably, about 20-40% by weight filler, based on the weight of the final composition, is employed. However, where the filler consists of one or more sugars alone, preferably about 20-30% of filler is used.

[0013] After the above mixture is milled, it is passed through a mesh screen along with the HPMC and a disintegrant/binder, and these are mixed together. The HPMC has a hydroxypropyl content of less than 9% and a molecular weight below 50K. Preferably, the molecular weight is below about 30K. A preferred HPMC is Methocel® K100LV (produced by Dow Chemical Co. of Midland, MI) which has a viscosity of about 100cps for a 2% solution. Preferably about 20-40% HPMC is used, more preferably about 25-30%.

[0014] A preferred disintegrant/binder is microcrystalline cellulose. Suitable microcrystalline cellulose products include Emcocel® (produced by the Edward Mendell Co. of Patterson, NY) Avicel® (produced by FMC Corp. of Philadelphia, PA), and mixtures thereof. In a preferred embodiment, about 25-50%, by weight of the final composition, of microcrystalline cellulose is used, more preferably about 25-30%. Not more than a combined amount of about 80% of disintegrant/binder and HPMC should be used. Also, the amount of microcrystalline cellulose should not substantially exceed that of HPMC, e.g., by more than 20-25%.

[0015] After the above components are mixed together, a lubricant is added and the composition is thoroughly mixed. Preferred lubricants include sodium stearyl fumarate and metal stearates, alone or in combination with stearic acid. More preferred lubricants include magnesium stearate, zinc stearate, calcium stearate, and mixtures thereof, alone or in combination with stearic acid. Preferably about 0.2-2%, by weight of the final composition, of lubricant is used, more preferably about 0.25-1.25%. For example, where magnesium stearate is the sole lubricant, the composition preferably comprises about 0.3-0.5% lubricant; where a magnesium stearate-stearic acid mixture is used as the lubricant, about 0.25% magnesium stearate may be combined with as much as about 1% stearic acid.

[0016] After the composition has been thoroughly mixed, it is directly compressed to form tablets, i.e. any solid form, e.g., caplets. These are then coated with a pharmaceutically acceptable coating. Preferred coatings include cellulose ether-based coatings, such as HPMC-based coatings. A preferred coating is Opadry, produced by Colorcon, Inc. of West Point, PA. Preferably about 0.5-4% by weight of coating is used (in terms of weight added to the uncoated tablet), more preferably about 1-2%.

Example 1

[0017] 120 mg pseudoephedrine hydrochloride caplets were prepared as described above, using a Methocel K100LV matrix. These were administered, one each, to 12 human subject volunteers comprising Group A (the test group); 12 Sudafed® 12 Hour Caplets (Warner Wellcome Consumer Healthcare) were administered, one each, to 12 human subject volunteers comprising Group B (the comparison group). Plasma concentrations of the active ingredient were determined by capillary gas chromatography from blood samples drawn from each patient at 0, 1, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 16, 24, 30, and 36 hours post-administration.

[0018] This example demonstrates that the dry granulation, direct compression product of the present invention is bioequivalent to national brand, 12 hour release pseudoephedrine tablets.

[0019] Variations of the methods and resulting compositions described herein as the preferred embodiment of the invention may be apparent to those in this field once they have studied the above description. Such variations are considered to be within the scope of the invention, which is intended to be limited only to the scope of the claims and the reasonably equivalent ingredients and methods to those defined therein.

Claims

1. A method for producing extended release tablets comprising the steps of:

   mixing an active ingredient with a glidant and a filler to form a mixture;

milling the said mixture;
screening the said mixture together with about 20% to about 40% of a HPMC, having a hydroxypropyl content below 9% and a molecular weight below 50K, and about 25% to about 50% microcrystalline cellulose to form a combination;
mixing the said combination;
adding a lubricant to said combination to form a composition; and
directly compressing said composition to form tablets.

2. The method according to claim 1 further comprising the step of coating said tablets with a pharmaceutically acceptable coating.

3. The method according to claim 2 wherein said coating is selected one of the cellulose ether-based coatings.

4. The method according to claim 3 wherein said coating comprises about 0.5% to about 4% by weight of said composition.

5. The method according any preceding claim wherein said active ingredient is selected from the group consisting of pseudoephedrine and its pharmacologically acceptable salts.

6. The method according to claim 3 wherein said active ingredient is pseudoephedrine hydrochloride.

7. The method according to any preceding claim wherein said active ingredient is present in an amount sufficient to produce tablets each comprising about 120mg of said active ingredient.

8. The method according to any preceding claim wherein said glidant is selected from the group consisting of colloidal silica and precipitated silica.

9. The method according to any preceding claim wherein said composition comprises about 0.2% to about 2% by weight of said glidant.

10. The method according to any preceding claim wherein said filler is selected from the group consisting of dicalcium phosphate, tribasic calcium phosphate, directly compressible calcium sulfate, directly compressible mannitol, anhydrous lactose, flowable lactose, and mixtures thereof.

11. The method according to claim 10 wherein said filler is dicalcium phosphate.

12. The method according to any preceding claim wherein said composition comprises about 20% to about 40% by weight of said filler.

13. The method according to any preceding claim wherein said lubricant is selected from the group consisting of sodium stearyl fumarate, magnesium stearate, zinc stearate, calcium stearate, mixtures thereof, and mixture thereof with stearic acid.

14. The method according to any preceding claim wherein said composition comprises about 0.2% to about 2% of said lubricant.

15. The tablet produced according to a method of any preceding claim.

16. A dry granulated, direct compressed, extended release pharmaceutical tablet comprising an active ingredient, a glidant, a filler, about 20% to about 40% of a HPMC having a hydroxypropyl content below 9% and a molecular weight below 50K, about 25% to about 50% microcrystalline cellulose, and a lubricant.

17. The tablet according to claim 16 wherein said active ingredient is selected from the group consisting of pseudoephedrine and its pharmacologically acceptable salts.

18. The tablet according to claim 17 wherein said active ingredient is pseudoephedrine hydrochloride.

19. The tablet according to any of claims 16 to 18 wherein said active ingredient is present in an amount sufficient to produce tablets each comprising about 120mg of said active ingredient.

20. The tablet according to any of claims 16 to 19 wherein said glidant is selected from the group consisting of colloidal silica and precipitated silica.

21. The tablet according to any of claims 16 to 20 wherein said composition comprises about 0.2% to about 2% by weight of said glidant.

22. The tablet according to any of claims 16 to 21 wherein said filler is selected from the group consisting of dicalcium phosphate, tribasic calcium phosphate, directly compressible calcium sulfate, directly compressible mannitol, anhydrous lactose, flowable lactose, and mixtures thereof.

23. The tablet according to claim 22 wherein said filler is dicalcium phosphate.

24. The tablet according to any of claims 16 to 23 wherein said composition comprises about 20% to about 40% by weight of said filler.

25. The table according to any of claims 16 to 24 wherein said lubricant is selected from the group consisting of sodium stearyl fumarate, magnesium stearate, zinc stearate, calcium stearate, mixtures thereof, and mixture thereof with stearic acid.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

DOCUMENTS CONSIDERED TO BE RELEVANT

EP 98305529.4

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 6)
X	EP 0249587 A1 (ARTIEBOLAGET HÄSSLE) 16 December 1987 (16.12.87), claims 1,11-15, page 3, lines 33-65, examples 1,4,5.	16,21-25	A 61 K 9/22 A 61 K 47/38 A 61 K 31/135
Y	Claims 1,11-15,17.	1-4,7-15,18-20	
Y	DE 3733540 A1 (SANDOZ-PATENT-GMBH) 09 October 1986 (09.10.86), claims 1,3,15,16,20,21,25,26, page 5, lines 25-34, examples 1,2.	1-4,7-15,18-20	
A	US 4792452 A (HOWARD, J.R. et al.) 20 December 1988 (20.12.88), claims 1,8-15,19,20, column 3, lines 35-59, example 1.	1-25	TECHNICAL FIELDS SEARCHED (Int. Cl.6)
A	EP 0396404 A1 (SCHERING CORPORATION) 07 November 1990 (07.11.90), claims 1-7,9-13, page 3, lines 3-27, examples 1A,2A, 3A.	1-25	A 61 K
A	EP 0126453 A2 (MERRELL DOW PHARMACEUTICALS INC.) 18 May 1984 (18.05.84), example 3.	1,5,6,9-11,13-18,21-23,25	
A	US 4369172 A (SCHOR, J.M. et al.) 18 January 1983 (18.01.83), claims 1,13, column 1, line 19 - column 5, line 42,	1,5-7,12-19,21,24,25	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	11-11-1998	MAZZUCCO

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
O : non-written disclosure
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EUROPEAN SEARCH REPORT

Application Number

DOCUMENTS CONSIDERED TO BE RELEVANT

EP 98305529.4

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.6)
	column 7, lines 22-43.		
A	WO 85/04100 A1 (AMERICAN HOME PRODUCTS CORPORATION) 26 September 1985 (26.09.85), examples 2-4,6, page 4, line 8 - page 5, line 13.	1,2,8-14,16, 20-25	
A	EP 0284849 B1 (LEK) 04 August 1993 (04.08.93), claims 1,2, page 5, lines 3-30, examples 1,2.	1,7-9, 13-16, 19-21, 25	
A	EP 0664118 A1 (YOSHITOMI PHARMACEUTICAL INDUSTRIES, LTD) 26 July 1995 (26.07.95), claim 1, examples 2,3,8-10, page 4, lines 21-35, page 5, lines 14-20, page 5, lines 32-35.	1-7,9, 10,12-19,21, 22,24, 25	TECHNICAL FIELDS SEARCHED (Int. Cl.6)
A	EP 0700680 A1 (BRISTOL-MYERS SQUIBB COMPANY) 13 March 1996 (13.03.96), claims 1-8,12,13, page 4, scheme.	1-4,7-10,12-16,19-22,24, 25	

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